Comparison of Gallium-67 Citrate and Technetium-99m Glucoheptonate in the Evaluation of Pulmonary Malignancies

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Sixty-five patients with suspected or proven pulmonary malignancy were examined with [^{67}Ga]citrate and [^{99m}Tc]glucoheptonate ([^{99m}Tc]GH) scintigraphy. In the final diagnosis 39 had primary lung carcinoma, four metastases in lung, mediastinum, and pleura from carcinomas elsewhere, and 22 benign pulmonary diseases. The sensitivity in the detection of pulmonary malignancies was 91% with ^{67}Ga and 95% with [^{99m}Tc]GH. The intensity of uptake was somewhat greater with ^{67}Ga than with [^{99m}Tc]GH in almost all malignant lung tumor groups. The specificity to detect malignant tumors was 82% with both radiopharmaceuticals. Irradiation and chemotherapy seemed to decrease ^{67}Ga uptake but not [^{99m}Tc]GH uptake. Only four of 22 benign diseases showed accumulation of both ^{67}Ga and [^{99m}Tc]GH. The intensity of uptake in benign processes was almost equal with that in malignant diseases, but most malignant processes were better delineated than the benign lesions. There were many differences between ^{67}Ga and [^{99m}Tc]GH uptake, which suggest different mechanisms of accumulation of these agents. It is concluded that some ^{67}Ga studies could be replaced by cheaper and more practical [^{99m}Tc]GH.

J Nucl Med 28:442–446, 1987

Gallium-67 (^{67}Ga) citrate is the most widely used radiopharmaceutical in tumor detection. Technetium-99m glucoheptonate ([^{99m}Tc]GH) also accumulates in lung tumors (*1,2*). Because using [^{99m}Tc]GH is much easier than using ^{67}Ga we have compared these agents in the present study in order to evaluate the possibility of using [^{99m}Tc]GH instead of ^{67}Ga in lung tumor detection.

MATERIAL AND METHODS

Sixty-five patients with pulmonary malignancy were studied with ^{67}Ga and [^{99m}Tc]GH scanning. Thirty-nine had proven bronchogenic carcinomas. Twenty-seven of them were detected histologically from tissue samples obtained in bronchoscopy or thoracotomy. Four had lung or pleural metastases from histologically proven carcinomas and 22 had benign diseases. All but one of the primary, all secondary lung malignancies, and all benign processes were radiographically visible. Bronchoscopy was performed in 35/39 patients with primary lung carcinoma.

Anterior, posterior, and lateral lung scans were made using a large field-of-view gamma camera 5–6 hr after i.v. injection of 20 mCi of [^{99m}Tc]GH and 48 hr after i.v. administration of 3 mCi of ^{67}Ga. Scintigrams were interpreted independently by three examiners without knowing the final diagnosis. Intensity of uptake was graded from 0–3: 0 = equal to lung parenchyma; 1 = weak activity; 2 = moderate; 3 = strong activity. The interpretation was mostly equal with all examiners. In three cases one examiner had interpreted weak uptake and the others had seen no uptake and in the final interpretation these (all with benign disease) were interpreted as 0.

Sensitivity is defined as a percentage of tests read as abnormal in patients with proven primary lung carcinoma or lung metastases. Specificity is the percentage of tests read as normal in patients free of malignant lung disease.

RESULTS

Tables 1, 2, and 3 present the results of our examination. The intensity of uptake was somewhat greater with ^{67}Ga than with [^{99m}Tc]GH in all malignant lung lesions, but the differences were not significant ($p > 0.05$ by paired Student's t-test) as shown in Table 1. On

Received Mar. 31, 1986; revision accepted Sept. 10, 1986.

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TABLE 1
Results of [^{99m}Tc]Glucoheptonate and [^{67}Ga]Citrate Scintigrams in Malignant Lung Lesions

Cell type	No. of patients	Positive		Sensitivity (%)		Visualization			Intensity (mean ± s.d.)	
						Better with				
		^{67}Ga	[^{99m}Tc]GH	^{67}Ga	[^{99m}Tc]GH	^{67}Ga	[^{99m}Tc]GH	Equal	^{67}Ga	[^{99m}Tc]GH
Squamous cell	27	25	26	93	96	10	7	10	1.86 ± 0.88	1.65 ± 0.62
Adenocarcinoma	6	5	6	83	100	3	2	1	1.89 ± 1.15	1.61 ± 0.57
Small cell	6	5	5	83	83	1	2	1	2.00 ± 0.79	1.94 ± 0.85
Metastatic carcinoma*	4	3	3	75	75	2	1	1	1.42 ± 1.17	1.17 ± 1.27
Totals	43	39	41	91	95	16	12	15	1.84 ± 0.91	1.64 ± 0.72

* Positive: one prostatic adenocarcinoma, one renal adenocarcinoma, one transitional cell carcinoma of bladder, Negative: rectal adenocarcinoma.

the other hand, two primary carcinomas of lung were negative with ^{67}Ga but positive with [^{99m}Tc]GH. The visualization of tumor was better with ^{67}Ga in 16 cases, with [^{99m}Tc]GH in 12 cases and equal with both radiopharmaceuticals in 15 cases. Examples of different uptakes are seen in Figures 1–2. Sensitivities to detect malignancies were with ^{67}Ga 91% and with [^{99m}Tc]GH 95%, and specificity was 82% with both radiopharmaceuticals. One squamous cell carcinoma and one metastasis of rectal adenocarcinoma were negative with both radiopharmaceuticals but the diameter of them was only ~1½ cm. One squamous cell carcinoma in the left hilus was weakly positive with both ^{67}Ga and [^{99m}Tc]GH but negative in chest radiograph. Bronchoscopy was positive in 23 of 35 primary pulmonary carcinomas (66%) and negative in 12 (34%).

Six patients had been given both irradiation and chemotherapy before imaging (Table 2). The intensity of uptake seemed to decrease to rather low level with ^{67}Ga but remained almost unchanged with [^{99m}Tc]GH.

Of 22 patients with benign lung disease, four showed accumulation of both radiopharmaceuticals in the lesions seen radiographically (Table 3). Only one of the nonvisualized benign processes was ~1 cm in diameter and thus too small to be detected with radiopharmaceuticals, three were ~2 cm in diameter and the remaining 14 were larger. In the positive cases the intensity of uptake did not differ from that of malignancies. Three had clearly greater uptake with ^{67}Ga than with [^{99m}Tc]GH. Only one case showed a rather sharply delineated focus (Fig. 3) but in the other three cases the activity was not delineated as sharply as in most malignancies.

Gallium-67 accumulated in bone but no marked accumulation of [^{99m}Tc]GH in bone was seen. In addition, four bone metastases in ribs and vertebrae took up ^{67}Ga but not [^{99m}Tc]GH. Tumors in the hilar region especially in the left hilus, were better visible with ^{67}Ga than with [^{99m}Tc]GH. Heart and great vessels make some processes near them somewhat difficult to detect with [^{99m}Tc]GH but not with ^{67}Ga.

TABLE 2
Effect of Irradiation and Chemotherapy on the Intensity of Uptake of [^{67}Ga]Citrate and [^{99m}Tc]Glucoheptonate in Primary Lung Carcinoma

Patient group	No. of patients	Intensity of uptake (mean ± s.d.)	
		^{67}Ga	[^{99m}Tc]GH
Totals	39	1.89 ± 0.89	1.68 ± 0.65
No therapy	33	2.00 ± 0.85	1.70 ± 0.88
Irradiation and chemotherapy	6	1.28 ± 0.95	1.56 ± 0.46

DISCUSSION

Our data confirm the earlier finding in our hospital (*1*) verified by Passamonte et al. (*2*) that primary and metastatic lung malignancies accumulate [^{99m}Tc]GH. We have also demonstrated that the sensitivity and specificity of [^{99m}Tc]GH and ^{67}Ga are almost equal to detect malignant lesions in lung. The sensitivity of ^{67}Ga to detect primary lung carcinoma is reported to be about same order: 84% (*3*) or 90% (*4*), as also that of [^{99m}Tc]GH: 88% (*1*) and 91% (*2*). Despite this finding, the sensitivity was somewhat better with [^{99m}Tc]GH (95%) than with ^{67}Ga (91%) we do not suggest that

TABLE 3
Results of [^{99m}Tc]Glucoheptonate and [^{67}Ga]citrate Scintigrams in Benign Lung Lesions

Disease	No. of patients	Positive	
		^{67}Ga	[^{99m}Tc]GH
Pneumonia	1	0	0
Tuberculosis	5	1	1
Pleural empyema	2	2	2
Pleuritis	1	0	0
Fibrosis	3	1	1
Lung infiltration	9	0	0
Pleural fibroma	1	0	0
Totals	22	4	4
Intensity of uptake	4	1.91 ± 1.10	1.33 ± 0.77

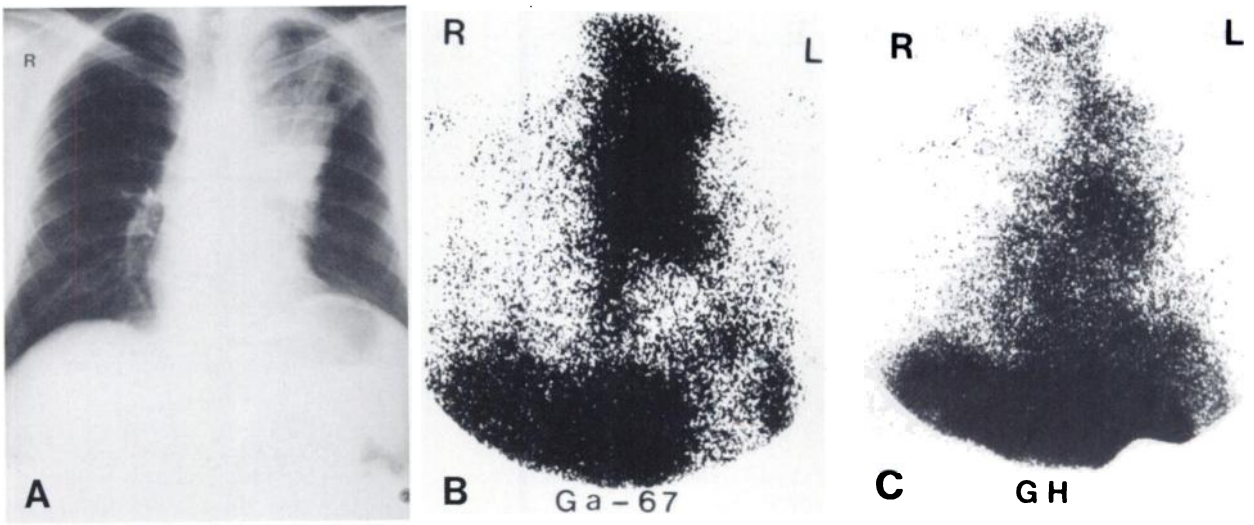

FIGURE 1
Squamous cell carcinoma in left hilus. Primary tumor and its supraclavicular metastasis accumulate ^{67}Ga greater than [^{99m}Tc]GH (GH).

[^{99m}Tc]GH should be better than ^{67}Ga in lung tumor detection. The difference in sensitivity was probably dependent on chance. On the other hand, the intensity of uptake was slightly greater with ^{67}Ga than with [^{99m}Tc]GH in almost all malignant groups.

The intensity of uptake of [^{99m}Tc]GH and also ^{67}Ga was greatest for small cell carcinoma and less for squamous cell and adenocarcinoma. In spite of the differences not being statistically significant our data supports the observation of Passamonte et al. (*2*) that the intensity of uptake is greatest for small cell carcinoma. Both primary tumors and their pulmonary metastases concentrated ^{67}Ga and [^{99m}Tc]GH differently on occasion but no logical system could be seen. For example one squamous cell carcinoma was markedly better visualized with ^{67}Ga and the other with [^{99m}Tc]GH. The explanation for this might be that there is considerable intermixing and overlapping between the four major categories of lung carcinomas: squamous cell carcinomas, adenocarcinomas, small cell carcinomas, and large cell carcinomas as reported by Saba et al. (*5*). They were able to show this overlapping of light microscopic categories using both electron microscopy and immunocytochemical method. It is therefore possible that using immunochemical methods and electron microscopy some logical explanation to the differences of uptake of ^{67}Ga and [^{99m}Tc]GH might be found.

It is known that both irradiation (*6*) and chemother-

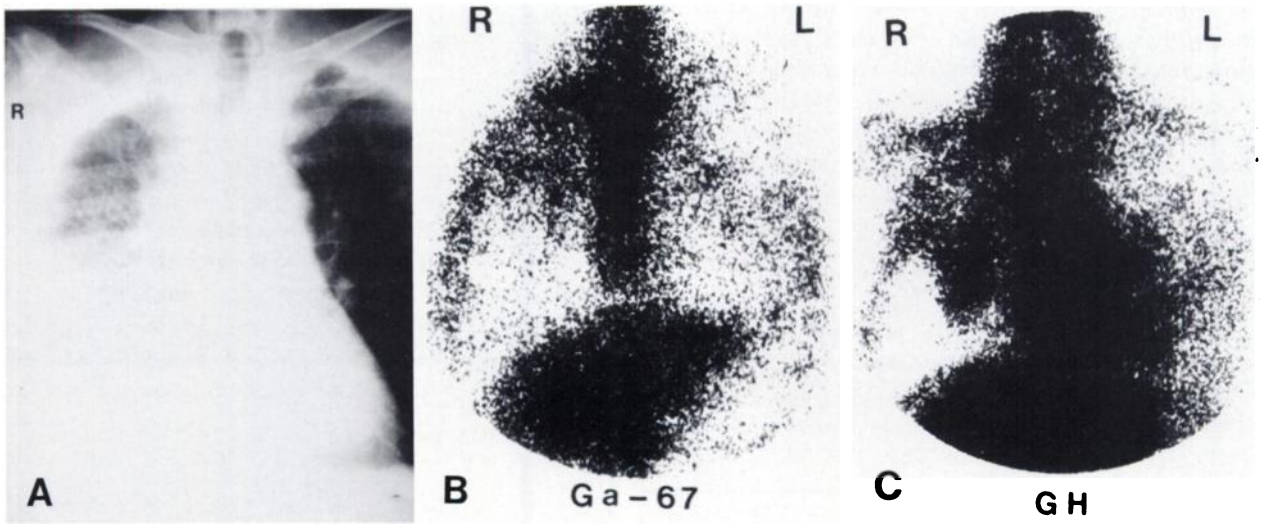

FIGURE 2
Adenocarcinoma in right hilus. Pleurisy with effusion makes the interpretation of radiograph difficult. The tumor can be seen nicely in [^{99m}Tc]GH image (GH) but not in ^{67}Ga image.

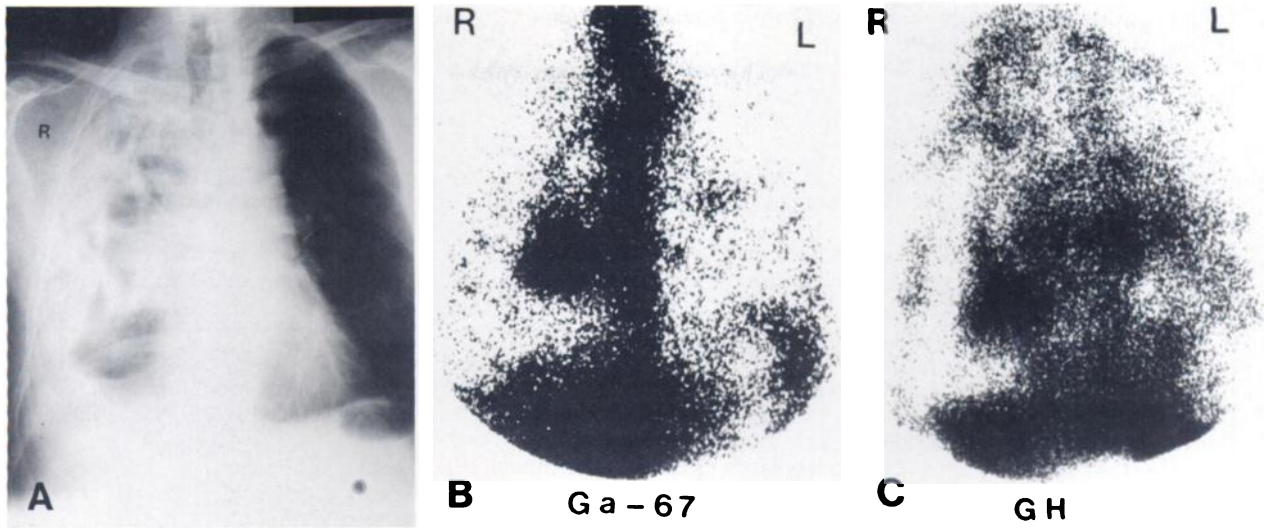

FIGURE 3
State after artificial pneumothorax. Pleural empyema verified in thoracotomy is sharply delineated and better visualized with ^{67}Ga than with [^{99m}Tc]GH (GH).

apy (*7*) decrease tumor uptake of ^{67}Ga. This was also noted in our study, in which both irradiation and chemotherapy were used for a small group of patients. However, no marked decrease of uptake of [^{99m}Tc]GH was seen. The cause must be the different mechanism of uptake of these radiopharmaceuticals.

Only four of 22 (18%) patients with benign diseases showed uptake of ^{67}Ga and [^{99m}Tc]GH. It is well-known that ^{67}Ga also accumulates in many benign processes (*8*). The small number of positive cases with [^{99m}Tc]GH disagrees with Passamonte's (*2*) results, in which almost all benign processes were noted to accumulate [^{99m}Tc]GH. In our study only patients with strong suspicion of malignancy were included. Thus active acute inflammatory processes were not studied. This may be the difference between our results and that of Passamonte's. The intensity of uptake seemed to be greater with ^{67}Ga than with [^{99m}Tc]GH in benign diseases. When an active focus is seen with ^{67}Ga or [^{99m}Tc]GH it seems, however, rather difficult to differentiate whether it is caused by a malignant or benign process. Mostly, however, malignant processes were better delineated on the image than benign processes.

Chest radiography was nonspecific but was, however, the most sensitive method in detecting both malignant and benign lung diseases and it is the most suitable screening method. The sensitivity of bronchoscopy in detecting primary lung carcinoma was only 66%, which is in agreement with common clinical knowledge. In the hilar region some tumors were better detected in ^{67}Ga and [^{99m}Tc]GH scans than in radiographs, and this finding agrees well with some earlier studies (*1,9,10*). Foci in the hilar region, especially in the left hilus, where the heart and great vessels interfere, were somewhat more visible with ^{67}Ga than with [^{99m}Tc]GH. On the other hand, some processes near bones were better seen in [^{99m}Tc]GH images. Some bone metastases simulated lung lesions in ^{67}Ga scans but not in [^{99m}Tc]GH scans.

The differences in uptake of ^{67}Ga and [^{99m}Tc]GH both in malignant and benign lung diseases, and different effect of therapy on the intensity of uptake suggest different mechanisms of accumulation of ^{67}Ga and [^{99m}Tc]GH. Although intensive investigation of the in vivo behavior of ^{67}Ga has been made, there is still no general agreement on the exact mechanisms of ^{67}Ga accumulation in either benign inflammatory or malignant lesions (*8*). Several mechanisms have been postulated such as increased permeability of cell membranes, association of gallium into cellular transport systems for calcium, and gallium transport by various iron transport systems (*8*). Likewise, the mechanism of uptake of [^{99m}Tc]GH is unknown. It has been suggested that [^{99m}Tc]GH, like a glucose analog, is taken up as a substrate for energy by metabolically active cells (*1,11*). Technetium-99m GH accumulates also in myocardial necrosis by unknown mechanism (*12*). It was not possible to get further explanation of the mechanisms of ^{67}Ga and [^{99m}Tc]GH uptake in the present study.

Because the sensitivity and specificity of ^{67}Ga and [^{99m}Tc]GH are almost equal, we recommend that the cheaper and more practical [^{99m}Tc]GH agent be utilized in place of ^{67}Ga until more specific agents are available.

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